

Symposium: Diet, Anthropometry and Breast Cancer: Integration of Experimental and Epidemiologic Approaches

Anthropometry and Breast Cancer¹

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ABSTRACT Relatively consistent findings about the relationships between body size and shape and breast cancer risk have been emerging in recent years. Adult height is predictive of breast cancer risk, even in populations with no evidence of energy or nutrient deficiency. A complex relationship with adiposity has been observed. The dominant pattern is increasing risk with increasing adiposity except in younger, premenopausal women from countries with high breast cancer rates, in whom an inverse association is noted. When adult weight is evaluated as a dynamic measurement rather than a constant one, excess weight in the years preceeding breast cancer diagnosis seems especially critical, consistent with the substantial evidence that adiposity at the time of breast cancer diagnosis is associated with an increased probability of recurrence and a decreased survival time. Adult weight gain has consistently predicted increased risk of breast cancer in older, postmenopausal women, even in some studies in which adult adiposity was only weakly associated with risk. In several studies, women with increased abdominal fat deposition, or central adiposity, also had an elevated risk of postmenopausal, though not necessarily premenopausal, breast cancer, independent of their adult adiposity. These patterns suggest that lifestyles leading to a positive energy balance are involved in the etiology of this disease and that energy intake and physical activity may be especially influential. The hormonal and metabolic mechanisms that account for these relationships between body size and shape and breast cancer risk are not adequately understood and merit further study. *J. Nutr.* 127: 924S-928S, 1997.

KEY WORDS: • *breast cancer* • *central adiposity* • *energy balance* • *height* • *weight*

Over 20 y ago, de Waard (1975) reviewed the epidemiologic research on weight, height and breast cancer in search of clues about the role of nutrition in breast cancer etiology. He postulated that the underlying mechanisms would involve endogenous hormones and metabolism. Since that time, however, epidemiologic and experimental research on breast cancer has focused on specific dietary factors, such as elevated fat intake, that might cause breast cancer. The importance of weight and height in human breast carcinogenesis is still controversial. Excess weight has been presented to the medical community as a weak and clinically unimportant determinant of breast cancer in postmenopausal women, and height as a risk factor that is not yet firmly established (Harris et al. 1992). However, recent reviews have suggested that height and adiposity (weight adjusted for height), along with weight change and patterns of fat deposition, merit more careful consideration (Ballard-Barbash 1994, Hunter and Willett 1993).

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HEIGHT

Adult height is predictive of breast cancer risk. In international comparisons, height is positively correlated with breast cancer incidence rates (Micozzi 1985). Both retrospective and prospective studies have frequently demonstrated clear associations between breast cancer risk and height (Ballard-Barbash 1994, Hunter and Willett 1993, Ziegler et al. 1996). Two retrospective studies, conducted in the early 1980s in the United States, primarily among white women, noted relative risks (RR)² of 2.1 and 1.7 for 13- and 18-cm increases in height, respectively. More recently, in the cohort of women examined in the first U.S. National Health and Nutrition Examination Survey (NHANES I), which oversampled women at risk for malnutrition, breast cancer risk, adjusted for accepted risk factors, was 90% higher among women in the highest quartile of height (mean height, 169 cm) than among women in the lowest quartile (mean, 153 cm) (P for trend = 0.03) (Swanson et al. 1988). In the cohort of women participating in the Breast Cancer Detection Demonstration Project, a screening program at 29 widely dispersed centers across the United States, tallness, whether directly measured or reported, was associated with increased breast cancer risk in women diagnosed at younger (<50 y) and older (50+ y) ages (Brinton

² Abbreviations used: CI, confidence interval; NHANES I, first National Health and Nutrition Examination Survey; RR, relative risk.

TABLE 1

Relative risks¹ (RR) of breast cancer by height in women participating in a U.S. multicenter breast cancer screening program²

	Height (inches) ³					P for trend
	<62	62–63	64–65	66–67	68+	
Women <50 y at diagnosis						
Reported height						
RR	1.0	1.18	1.38	1.68	1.83	0.009
Number of cases	(33)	(92)	(134)	(109)	(46)	
Measured height						
RR	1.0	1.36	1.44	1.54	1.51	0.01
Number of cases	(32)	(93)	(127)	(100)	(37)	
Women 50+ y at diagnosis						
Reported height						
RR	1.0	1.14	1.20	1.39	1.47	0.008
Number of cases	(145)	(308)	(327)	(251)	(84)	
Measured height						
RR	1.0	1.05	1.19	1.32	1.59	0.003
Number of cases	(151)	(297)	(328)	(240)	(78)	

¹ Adjusted for age at diagnosis, age at menarche, and education. Age at first childbirth/nulliparity, family history of breast cancer, history of breast biopsies, age at menopause, alcohol consumption, and years of menopausal hormone use were not important confounders.

² A total of 1529 breast cancer patients and 1901 control subjects were included in the analyses. Data from Brinton and Swanson (1992).

³ Cutpoints correspond to 1.51, 1.56, 1.61, 1.64, and 1.66 m.

and Swanson 1992). The adjusted RR for women at least 173 cm in height were 1.5–1.8 the risk of women less than 158 cm in height (Table 1). However, other studies conducted in the United States, such as the prospective Nurses' Health Study (London et al. 1989) and the retrospective Cancer and Steroid Hormone Study (Chu et al. 1991) have reported modest or no associations between breast cancer and height.

In our population-based case-control study of breast cancer among Asian-American women, height was strongly predictive of breast cancer risk, even after adjustment for accepted breast cancer risk factors (Ziegler et al. 1996). Risk doubled (RR = 2.0) over the 18-cm range in height (from ≤ 151 cm to ≥ 166 cm) (P for trend = 0.003), with comparable effects in premenopausal and postmenopausal women. This study, conducted among women of Chinese, Japanese, and Filipino ethnicity, 20 to 55 y of age and living in San Francisco-Oakland and Los Angeles (California) and Oahu (Hawaii), was designed to take advantage of the diversity in lifestyle and breast cancer risk in these migrant populations. Breast cancer incidence rates have historically been four to seven times higher in the United States and many other Western countries than in Asia. When Chinese, Japanese or Filipino women migrate to the United States, their risk of breast cancer rises over several generations and reaches that for U.S. white women (Ziegler et al. 1993), indicating that modifiable exposures, related to lifestyle or environment, are involved. Within our study population, we have demonstrated a sixfold gradient in breast cancer risk by migration history, comparable to the international differences in breast cancer incidence rates (Ziegler et al. 1993).

It is frequently assumed that height is related to breast cancer risk only in those populations in which inadequate intake of energy and nutrients in childhood and adolescence limits growth, such as developing countries and European nations coping with food shortages during World War II (London et al. 1989, Tretli 1989). This explanation is consistent with numerous animal experiments demonstrating that energy intake restriction inhibits both spontaneous and induced mammary carcinogenesis (Tannebaum and Silverstone 1953). Furthermore, because events during childhood and adolescence

determine adult height, early exposures, possibly affecting mammary mass (Albanes and Winick 1988), may also be critical in breast carcinogenesis (Hunter and Willett 1993, Swanson et al. 1988). Recently, it has been postulated that height reflects the total number of ductal stem cells that develop in the breast in utero and thus the importance of prenatal exposures (Trichopoulos and Lipman 1992).

However, an enhanced risk of breast cancer among taller women has been demonstrated in populations, such as the United States population, in which energy or nutrient deficiency is not evident and tallness is determined primarily by genetic factors (Ballard-Barbash 1994, Hunter and Willett 1993, Ziegler et al. 1996). Thus it is possible that inherited patterns in endogenous hormones and growth factors contribute to the height attained prior to epiphyseal closure at puberty and also to the promotion of breast carcinogenesis, either at puberty when breast tissue is rapidly developing or at a later stage in the life cycle. Estrogen and progesterone are generally believed to be the hormones that determine breast cancer risk (Bernstein and Ross 1993), but androgens, growth hormones, insulin and insulin-like growth factors deserve consideration. In addition, dietary exposures other than energy deprivation may influence height; an overabundance of energy and fat and variation in macronutrient intake in the years prior to puberty may play a role.

ADIPOSIITY

A complex relationship with adiposity has been observed in many of the epidemiologic studies of breast cancer conducted in Western countries; as adiposity increases, risk also increases in older, postmenopausal women but decreases in younger, premenopausal women (Ballard-Barbash 1994, Hunter and Willett 1993). In the Nurses' Health Study cohort, premenopausal women in the highest quintile of adiposity had 60% the risk of women in the lowest quintile (P for trend <0.001) whether adult weight (≥ 29 kg/m² relative to <21 kg/m²) or recalled weight at age 18 y (≥ 25 kg/m² relative to <20 kg/m²) was used (London et al. 1989). Although no clear relationship with adiposity was seen in all postmenopausal

women combined, in the oldest women in the cohort (55–64 y of age), risk was 40% higher among the women currently the heaviest ($\geq 29 \text{ kg/m}^2$) relative to the lightest ($< 21 \text{ kg/m}^2$) (P for trend = 0.51). In the Iowa Women's Study cohort, which included only postmenopausal women (55–69 y at baseline), risk was elevated 50% among women in the highest quintile of adiposity ($\geq 30.7 \text{ kg/m}^2$) relative to women in the lowest quintile ($\leq 22.9 \text{ kg/m}^2$), when analysis was restricted to women with no family history of breast cancer (Sellers et al. 1992). Among women with a family history, a more striking increase in risk with adiposity was suggested. Age-specific results from several other epidemiologic studies of breast cancer indicate that the positive association with adiposity in postmenopausal women may be either limited to or strongest among the oldest postmenopausal women (London et al. 1989).

The inverse association between adiposity and breast cancer in younger women was initially attributed to earlier detection of breast tumors in leaner women, but further analyses that considered tumor stage did not support this hypothesis (Brinton and Swanson 1992, London et al. 1989). At present, hormonal mechanisms are being evaluated, specifically whether heavier premenopausal women have more anovulatory menstrual cycles, resultant decreases in estrogen and progesterone exposure, and lower luteal phase progesterone levels in ovulatory cycles (Key and Pike 1988).

In our breast cancer study in Asian-American women, the dominant pattern was increasing risk with increasing adiposity (Ziegler et al. 1996). Among women in their 40s and in their 50s, risk more than doubled when extreme deciles of usual adult adiposity³ were compared ($> 31.3 \text{ kg/m}^{1.5}$ vs. $< 22.9 \text{ kg/m}^{1.5}$) (P for trend = 0.05 for both age groups). Only in the heaviest of the youngest women ($> 29 \text{ kg/m}^{1.5}$ and < 40 y) was breast cancer risk substantially reduced. Thus the positive association with adiposity observed among the Asian-American women was stronger and apparent at younger ages than in other U.S. studies of breast cancer, in which RR generally range from 1.0 to 1.5 in postmenopausal women (Ballard-Barbash 1994, Hunter and Willett 1993, Ziegler et al. 1996). Our findings are consistent with a meta-analysis of case-control data from countries at high, moderate and low risk for breast cancer, which demonstrated that breast cancer incidence rates consistently increased with adiposity among both premenopausal and postmenopausal women except for premenopausal women from high risk countries, where an inverse relationship was noted (Pathak and Whittemore 1992).

Most epidemiologic studies of breast cancer have utilized a single static measure of adult weight. However, in many women, weight fluctuates during adult life, and the timing and magnitude of such changes may be crucial in understanding their importance in cancer etiology (Ballard-Barbash 1994). In our study of Asian-American women, we asked about usual weight during each decade of adult life, excluding the most recent 3 y. Therefore, we could examine the influence of adiposity at different periods over a lifetime and at different stages of carcinogenesis (Ziegler et al. 1996). Recent adiposity influenced breast cancer risk more than earlier adiposity. For women in their 50s (Table 2) and in their 40s (data not shown), positive trends in risk with increasing adiposity became more striking as the decade in which breast cancer was diagnosed was approached. We wanted to determine whether

the remarkable effect of excess weight in the years immediately preceding breast cancer diagnosis that we observed was suggested in other studies and other populations, but we have been unable to find other breast cancer studies that evaluated recent adiposity in older women.

The critical importance of excess weight in the years preceding breast cancer diagnosis is consistent with the many recent reports showing that adiposity at the time of breast cancer diagnosis is associated with an increased probability of recurrence and a decreased survival time, even after adjusting for stage and treatment (Ballard-Barbash 1994, Senie et al. 1992, Tretli et al. 1990). If adiposity can enhance tumor growth after diagnosis, it should be expected to promote tumor development and growth also in the late stages of breast carcinogenesis prior to clinical detection.

WEIGHT CHANGE

In both retrospective and prospective studies, adult weight gain has consistently predicted increased risk of breast cancer in older, postmenopausal women, even in studies in which adult adiposity was only weakly associated with breast cancer risk. For example, in the Nurses' Health Study cohort, a net gain of $> 20 \text{ kg}$ between age 18 y and the most recent follow-up was associated with a 40% increase in risk [RR = 1.4, 95% confidence interval (CI) = 1.0 to 2.0] in postmenopausal women and a 40% decrease in risk (RR = 0.6, 95% CI = 0.4 to 0.9) in premenopausal women, relative to women with no weight change (London et al. 1989). In the NHANES I cohort, maximum adult change in adiposity was predictive of increased risk of breast cancer (Ballard-Barbash et al. 1990b), even though adiposity at baseline was not (Swanson et al. 1988). Initially, adult weight gain was believed to be a more accurate measure of increased body fat than adult adiposity measured at one point in time. More recently, it has been suggested that weight gain during especially susceptible periods in breast carcinogenesis, such as pregnancy or menopause, may be especially critical, or that weight gain during these periods of hormonal transition may indicate high risk metabolic patterns (Ballard-Barbash 1994).

In our study of Asian-American women, adult weight gain was associated with increased breast cancer risk for women in their 40s and 50s; however, further analyses suggested that it was primarily important as a determinant of adiposity in the years preceding diagnosis (Ziegler et al. 1996). Recent weight change, (between the current and preceding decade) was more predictive of breast cancer risk than adult weight change. For women in their 50s, a recent gain of more than 10 pounds was associated with a doubling of risk (RR = 2.3), relative to no recent weight change (P for trend = 0.002). Recent weight loss was associated with a reduced risk of breast cancer in all age groups (RR approximately 0.7), relative to no change in weight. Although the effects of adiposity and weight change in the decade preceding diagnosis were not totally independent, neither measure fully explained the effect of the other.

The importance of recent weight gain and recent adiposity in these Asian-American women suggests that excess weight may function as a late stage promoter of breast carcinogenesis. Whether our findings in Asian-American women can be generalized is not a simple question (Ziegler et al. 1996). Asian-American women are leaner than other U.S. women. They adhere to distinctive dietary and physical activity patterns. The protective influence of adiposity in early adult life is minimal in this population. However, genetics is not the explanation, because these Asian-American women acquire the high breast cancer rates of U.S. whites after several generations of acculturation.

³ In these Asian-American women, as in many other female populations, weight/height^{1.5} was more strongly correlated with weight and concurrently less strongly correlated with height than weight/height^{2.0} and was thus selected as a better measure of adiposity (Ziegler et al. 1996).

TABLE 2

Relative risks¹ (RR) of breast cancer by adiposity during specific decades of adult life in Asian-American women in their 50s

	Decade-specific adiposity ²				P for trend
	Lowest 20%	21–50%	51–79%	Highest 20%	
Weight in 50s/height ^{1.5}					
RR	1.0	1.14	1.96	2.13	0.004
No. cases/controls	(32/68)	(38/85)	(75/92)	(51/61)	
Weight in 40s/height ^{1.5}					
RR	1.0	1.21	1.72	1.92	0.02
No. cases/controls	(29/59)	(57/104)	(71/94)	(40/48)	
Weight in 30s/height ^{1.5}					
RR	1.0	1.34	1.63	1.70	0.08
No. cases/controls	(31/63)	(63/101)	(66/90)	(36/49)	
Weight in 20s/height ^{1.5}					
RR	1.0	1.06	1.28	1.32	0.29
No. cases/controls	(30/55)	(60/98)	(66/96)	(36/51)	

¹ Adjusted for ethnicity, study center, age at first live birth, family history, and history of benign breast disease. Age at menarche, menopausal status, and parity were not confounders.

² Stratified according to the frequency distribution of decade-specific weight/height^{1.5} among all the controls. The 20th, 50th and 80th percentiles for controls in their 50s, 40s, 30s and 20s, respectively, were 25.3, 27.3 and 30.8 kg/m^{1.5}; 24.7, 27.0 and 30.3 kg/m^{1.5}; 23.5, 25.9 and 28.7 kg/m^{1.5}; and 22.5, 24.7 and 27.1 kg/m^{1.5}. These relative weights imply, for a woman at the median height in this Asian-American population of 62 in, weights of 110, 119 and 134 lb for women in their 50s; weights of 108, 118 and 132 lb for women in their 40s; weights of 103, 113 and 125 lb for women in their 30s; and weights of 98, 108 and 118 lb for women in their 20s. Data from Ziegler et al. (1996).

FAT DEPOSITION PATTERNS

Several studies have reported that women with increased abdominal fat deposition, or central adiposity, also have an increased risk of postmenopausal, (though not necessarily premenopausal) breast cancer, independent of their adult adiposity. In the Iowa Women's Health Study, women in the highest quintile of waist-to-hip circumference ratio had a risk 1.5 times that of women in the lowest quintile (P for trend = 0.005), and this relationship was especially strong among women with a family history of breast cancer (Sellers et al. 1992). In the Framingham cohort, a ratio of trunk-to-extremity skinfold thicknesses was associated with a 70% increase in risk (P for trend = 0.14) (Ballard-Barbash et al. 1990a). The abdominal pattern of fat deposition, which is believed to be genetically determined, has been linked to diabetes mellitus, hypertension and cardiovascular disease. Abdominal adiposity has been associated with androgen excess (Kirschner et al. 1990); other hormonal and metabolic patterns that it either indicates or causes are being identified (Ballard-Barbash 1994).

Mechanisms that might account for the relationship of adult adiposity, adult weight gain, abdominal fat deposition and breast cancer in older, postmenopausal women—a relationship demonstrated in many epidemiologic studies—have been proposed but not proven. Estrogen production in adipose tissue from circulating androgens is elevated in heavy women, may promote tumor growth, and becomes increasingly important as ovarian estrogen production diminishes with age (Bernstein and Ross 1993, Key and Pike 1988). The effect could be localized, with especially high estrogen levels near breast adipose tissue. In addition, the decreased sex hormone-binding globulin levels and the increased triglyceride levels associated with excess weight increase the bioavailability of estrogen (Ballard-Barbash 1994). Alternatively, the elevated levels of insulin and growth factors associated with adiposity may promote tumor growth, either directly or by modulating steroid activity (Bruning et al. 1992, Stoll and Sretero 1992).

Relatively consistent associations between anthropometric measures, specifically height, adiposity, weight gain and body fat deposition, and breast cancer risk have been emerging in

recent years. The patterns suggest that lifestyles leading to a positive energy balance are involved in the etiology of breast cancer and that energy intake and physical activity may be more critical than dietary fat. Many unanswered questions about anthropometric exposures remain for the epidemiologists: whether there are especially susceptible periods in the lifespan or in breast carcinogenesis, how body size and shape interact with a family history of breast cancer and with reproductive and menstrual risk factors, over what ranges of body size and shape are effects on breast cancer seen. However, experimentalists will need to identify the hormonal and metabolic mechanisms underlying the epidemiologic associations. Experimental studies ranging in focus from the molecular level to the metabolic laboratory will be required. The challenge will be to enhance communication and collaboration between experimental and epidemiologic researchers so that the findings of each approach can be rigorously evaluated by the other.

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